Patent Claims

1. A fusion protein of the structure

F – (L)n – M,

having essentially the same biological specificity and activity of humanTPO, comprising an immunoglobulin heavy chain constant region (F) and a human TPO molecule (M) in a truncated (1 – 174) form modified by one or more amino acid substitutions, wherein said fusion protein is substantially non-immunogenic or less immunogenic than the parental fusion protein comprising the non-modified human TPO, and said amino acid substitutions have been carried out in one or more of the sequence tracks

(i) GEWKTQMEETKAQDILGAVTLLLEGVM,

(ii) PTTAVPSRTSLVLTL

within the truncated wild-type TPO molecule and cause a reduction or an elimination of one or more of T-cell epitopes, which act in the parental non-modified fusion molecule as MHC class II binding ligands and stimulate T-cells,

said immunoglobulin heavy chain constant region is fused directly (n = 0) or indirectly (n = 1) via a linker molecule (L) to said modified human TPO molecule (M).

2. A fusion protein according to claim 1, wherein F is an Fc domain.

3. A fusion protein of claim 1 or 2, wherein F comprises a hinge region.

4. A fusion protein according to any of the claims 1 – 3, wherein the C-terminus of the human immunoglobulin heavy constant region domain is linked directly or indirectly to the N-terminus of the modified TPO molecule.

5. A fusion protein according to any of the claims 1 – 4, wherein said modified TPO molecule contains one or more of the amino acid substitutions

M55K, A60R and V161A

within the sequence tracks (i) – (ii).

6. A fusion protein according to any of the claims 1 – 4, wherein said TPO molecule in said fusion protein has the formula / structure:

SPAPPACDLRVLSKLLRDSHVLHSRLSQCPEVHPLPTPVLLPAVDFSLGX^1X^2KTQX^3EEX^4KX^5X^6D
X^7LGAX^8TX^9L$X^{10}X^{11}$GVMAARGQLGPTCLSSLLGQLSGQVRLLLGALQSLLGTQLPPQGRTTAHKDP
NAIFLSFQHLLRGKVRFLMLVGGSTLCVRRAPPTTA$X^{12}X^{13}$SRTSLVLTLNEL

X^1 is A, E;

X^2 is S, W;

X^3 is A or T or K, S or M;

X^4 is A, T;

X^5 is R, A;

X^6 is A or T or Q;

X^7 is A or T or I;

X^8 is A or T or V;

X^9 is A or T or S or L;

X^{10} is A or L;

X^{11} is A or S or E;

X^{12} is N or A or T or R or E or D or G or H or P or K or Q or V;

X^{13} is A or P,

and whereby simultaneously $X^1 = E$, $X^2 = W$, $X^3 = M$, $X^4 = T$, $X^5 = A$, $X^6 = Q$, $X^7 = I$, $X^8 = V$, $X^9 = L$, $X^{10} = L$, $X^{11} = E$, $X^{12} = V$ and $X^{13} = P$ are excluded.

7. A fusion protein according to any of the claims 1 – 6, wherein F is in Fc domain of human IgG4.

8. A fusion protein according claim 7, wherein L is a peptide linker having 4 – 20 amino acid residues.

9. A fusion protein according to any of the claims 1 – 8, selected from the group consisting of
F – M1 to F – M67,
F – L – M1 to F – L – M67, and
F1 – L – M1 to F1 – L1 – M67,
wherein F is an immunoglobulin heavy chain constant region, L is a linker peptide, F1 is a Fc domain of human IgG4 comprising a modified hinge region, L1 is a peptide linker having the sequence GAGGGGSGGG GSGGGSG, and M1 – M67 are modified TPO sequences as specified in Table A1.

10. A fusion protein according to claim 9 selected from the group consisting of
F – M1, F – L – M1, F1 – L1 – M1
F – M66, F – L – M66, F1 – L1 – M66, and
F – M67, F – L – M67, F1 – L1 – M67.

11. A dimeric fusion protein comprising two identical monomeric fusion protein chains according to any of the claims 1 – 10.

12. A peptide molecule selected from the group consisting of
(i) GEWKTQMEETKAQDILGAVTLLLEGVM,
(ii) PTTAVPSRTSLVLTL
or a sequence track consisting of at least 9 consecutive amino acid residues of any of said peptide molecules having a potential MHC class II binding activity and created from the primary sequence of non-modified human TPO, whereby said peptide molecule or sequence track has a stimulation index of > 1.8 in a biological assay of cellular proliferation and said index is taken as the value of cellular proliferation scored following stimulation by a peptide and divided by the value of cellular proliferation scored in control cells not in receipt peptide.

13. Use of a peptide molecule according to claim 12 for the manufacture of a vaccine in order to reduce immunogenicity to TPO in a patient.

14. A peptide molecule modified by one or more amino acid substitutions deriving from any peptide molecule according to claim 11 and having a reduced or absent potential MHC class II binding activity expressed by a stimulation index of less than 2, whereby said index is taken as the value of cellular proliferation scored following stimulation by a peptide and divided by the value of cellular proliferation scored in control cells not in receipt peptide.

15. Use of a modified peptide molecule according to claim 14 for the manufacture of a modified TPO molecule M1 to M67 of Table A1, or a fusion protein comprising an Fc portion of an immunoglobulin and said modified TPO molecule.